



# Preoperative Radiation in the Treatment of Cancer

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■ *In the treatment of advanced cancer of the hypopharynx, preoperative radiation therapy has proven to be of value for the prevention of recurrences in the operative area following radical neck dissection for cancer of the head and neck. Also it has been of value in the planned combined therapy of certain patients with lung, bladder, breast, esophagus, bone, endometrial and rectal cancers.*

*Preoperative radiation therapy should be advantageous in patients who have malignant disease where the possibility exists for the cancer cells to be disseminated during the surgical procedure.*

IN RECENT YEARS there has been increasing interest in the use of preoperative radiation therapy. The impression has been that if radiation is effective when given postoperatively, then the possibilities are that before operation, when the blood supply to the involved area has not been compromised and there has been no trauma, it may offer even greater benefits.

The availability of megavoltage equipment, permitting precise dosimetry, skin sparing, improved depth dose, less scattering of the beam and less differential absorption of the radiation in the various tissues of the body, has contributed to the effectiveness of such therapy. The training of the radiation therapist is constantly improving, and more physicians are specializing in the therapeutic

application of ionizing radiation with due concern for the complete medical care of the patient.

## Clinical Basis for Use

It is not always possible by known diagnostic methods to determine the full extent of the malignant disease. Cancer cells may already have spread beyond the operative field without any clinical evidence to indicate the extent of the disease.

Because of infiltration of cancer cells into the tissues locally, or as a result of the proximity to certain vital organs, complete removal of the cancer may not be possible.

In the presence of local edema and/or infection there may be a question whether the tumor is operable, as for example, in certain cases of breast cancer or carcinoma of the recto-sigmoid colon.

Cancer cells may remain in the operative area following the completion of the operation, or may have been disseminated during the surgical procedure.

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## Problem of Preoperative Irradiation

Among the problems associated with preoperative radiation therapy are the following:

- What is the optimum preoperative tumor dose, and the period of time over which it should be given?
- Should the operation immediately follow completion of the preoperative radiation therapy, and, if not, then what is the optimum delay?
- To what extent may preoperative radiation therapy cause undesirable delay in operation?
- What are the possibilities for an increase in morbidity, or complications or delay in wound healing, or in mortality, when preoperative radiation therapy is given?
- How many viable cancer cells, capable of reproducing to produce recurrent metastatic disease, will remain in the operative area?

## Advantages

Following are some of the advantages of preoperative radiation therapy:

- When there is a question of operability or when there is a reasonable chance that it will not be possible to completely remove the tumor, preoperative radiation therapy may be of particular value.
- The incidence of recurrences in the operative area, when cancer cells remain following the operation, may be prevented or reduced.
- The viability and the ability to reproduce, of those cancer cells which may have been disseminated incidental to the trauma of the surgical procedure, will be diminished.
- An area considerably larger than that intended for surgical excision can be included in the radiation field.

## Effects

The direct effect of radiation upon the cancer cells is instantaneous and there may be ancillary advantages:

- The cancer cells may be either destroyed or rendered incapable of reproduction.
- The host's immune mechanism may be stimulated.
- Beneficial effects may be exerted on the cancer bed lymphatics, the blood supply, and the supporting tissues.
- Since they have a better blood supply, are younger and are dividing at a more rapid rate,

small nests of cancer cells and those located in the peripheral portions of the cancer are more radio-sensitive than those in the central mass or core. Any necrotic or anoxic cells in the central portion are more likely to be completely removed by surgical operation.

If a cancer is quite small, freely movable, and one which can readily be removed with a wide margin of surrounding tissue, the use of preoperative radiation therapy is probably not indicated. If metastasis has already occurred, then preoperative radiation therapy is certainly not justified.

## Data Based on Animal Studies

From experiments on mice, DeSault<sup>5</sup> and Kasenter presented evidence that irradiated tumors, even when not controlled by this therapy, grow more slowly than untreated tumors.

Feder<sup>6</sup> and associates attempted to answer certain questions as to the possible justification for a small dose of preoperative radiation, the importance of fractionation and the optimum period of delay between the time of radiation and resection. They expressed belief that sufficient scientific evidence has been presented in the literature for the justification of a small dose of preoperative radiation. They have also demonstrated that preoperative radiation in relatively small doses significantly reduced the transplantability of a C3H rhabdomyosarcoma to a C3H mouse. Laboratory investigations have been reported indicating that the growth potential of a tumor can be reduced by small doses of preoperative radiation. Feder<sup>6</sup> and coworkers believe that if preoperative radiation at higher dose levels is to be used clinically, the radiation therapist must still determine the optimum degree of fractionation in his effort to enhance the therapeutic ratio. At low dose levels preoperative radiation may be more effective if very little fractionation is employed.

Hoye<sup>7</sup> and Smith, in experiments with mice, attempted to reduce the number of tumor cells disseminated at operation, by treating the primary intact tumor 24 hours preoperatively with radiation or systemic TSPA in dosages that would be insufficient to stop the growth or cause regression of the primary tumor. The growth of tumor which was disseminated intravascularly, intramuscularly or into an axillary wound from the in vivo treated primary tumor was decreased by more than 90 percent.

Inch and McCredie<sup>8</sup> reported experiments in

which preoperative administration of a single dose of x-radiation (2,000 rads) to the carcinosarcoma 256 Walker mouse tumor, 24 hours before excision, caused a significant reduction in the number of local recurrences. They considered preoperative more effective than postoperative radiation because the tumor cells were still in situ before operation and the blood supply was still intact. For clinical application they recommended giving the small dose of radiation over a short period immediately preceding operation.

Suit<sup>18</sup> and Schiavone described an experiment to estimate the extent of transfer of cells out of the hypoxic compartment following a single radiation dose, or two doses, to a mouse mammary carcinoma with an intertreatment interval of five days. The results led them to believe that there is strong evidence that in some solid tumors the degree of the hypoxic fraction is not constant but is subject to change and does decrease during the course of the fractionated radiation.

In an experimental study using mice, reported by Vermund<sup>19</sup> and associates, inhibition of tumor growth was found to increase linearly with increasing doses to a maximum at about 3,000R. Larger doses do not produce a greater effect. When the tumor was transplanted to the brain, where a sparsity of connective tissue exists, no tumor bed effect was noted. The radiation-induced changes that give rise to the tumor bed effect remained present for at least nine months.

Powers<sup>16</sup> and coworkers reviewed a series of 214 patients who were operated on after radiation therapy and found no demonstration of an optimal dose of radiation, or of time interval between radiation and operation, to permit complete and adequate wound healing with minimum delay. Studies in animals revealed that small doses of radiation cause relatively little delay, whereas doses in the order of 4,000 rads caused considerable delay in healing in some of the animals.

Quantitative extrapolation of these and other animal data to human therapy should obviously not be attempted, but some qualitative trends may perhaps be suggested.

### Clinical Usefulness

Preoperative radiation therapy has proven to be of value in the treatment of patients with advanced cancer of the laryngopharynx, for the prevention of recurrences in the operative field following radical neck dissection for patients with head and

neck cancer, and in planned combined therapy of patients with lung, bladder, breast, uterus, bone, kidney and rectal cancers.

A "curative" course of radiation therapy has been advocated by some radiation therapists, with operation to follow in approximately six to eight weeks in order that the major effect from the ionizing radiation on both the cancer cells and the tumor bed would have taken place.

After a "curative" course of radiation therapy (approximately 6,000 rads given in approximately six weeks for epidermoid carcinoma) has been given, there may be an increase in postoperative complications, delay in wound healing, increased technical difficulties at operation, greater morbidity, and possibly some increase in mortality. Buschke<sup>2</sup> and Galante believe that high cancerocidal radiation doses can be given preoperatively when longer protraction and megavoltage radiation therapy are used and that the vasculoconnective tissues can be preserved. They gave preoperative radiation therapy to ten patients with cancer of the head and neck, using one million volt x-rays (3.2mm Pb. h.v.1.) and between 6,000 and 8,000 R (skin) in 32 to 39 days, for a minimal tumor dose of 4,100 to 6,500 R through one field. Operation was done in from one to five and one-half months after completion of the therapy. There were no surgical complications beyond those which one would anticipate when no preoperative radiation therapy was given.

### *In Carcinoma of the Lung*

My own experience has been that if preoperative tumor doses in excess of 4,000 rads in four weeks are given, the possibilities for increased morbidity, mortality and operative technical problems are increased. When tumor doses of 5,000 rads in five weeks were given preoperatively for the treatment of lung carcinoma, using x-rays from the 6 Mev linear accelerator, there was a definite increase in morbidity and mortality. After the initial experience of treating carcinoma of the lung preoperatively with this technique in 20 patients, the tumor dose was reduced to 4,000 rads in four weeks, and there was a decrease in morbidity and complications.

Bloedorn<sup>1</sup> expressed belief that the use of preoperative radiation may be effective in the treatment of bronchogenic carcinoma provided that a definite program of policies and techniques of treatment can be developed and that close coopera-

tion exists between all specialists concerned in the combined program.

Mallams<sup>11</sup> and coworkers, reporting on the results of a seven-year study utilizing preoperative radiation therapy followed by operation in four weeks for clinically diagnosed apparently localized bronchogenic carcinoma of the superior sulcus type, expressed an opinion that this may be the treatment of choice. Of 28 patients treated, two were alive after more than six years, and five of nine patients who were suitable for four-year evaluation were alive and well. Thirty-three percent of 24 patients were alive and well at the end of two years. The tumor dose given preoperatively varied from 3,000 to 3,500 rads given in 15 treatments during a period of 19 days. Mallams<sup>11</sup> held that increasing the radiation dose will result in more complications without increasing the survival rate. Paulson,<sup>15</sup> in 1967, said that of 34 patients with superior pulmonary sulcus carcinomas who completed combined therapy from 1956 through 1965, 12 had a five-year survival. There were two operative deaths and a minimum of complications. He was of the opinion that complete sterilization by radiation therapy is not necessary and may even be harmful because of the effect upon the normal tissue cells and the interference with the normal tissue reparative processes.

#### *In Carcinoma of Esophagus*

Nakayama<sup>14</sup> said he believed preoperative radiation should be given as an adjunct to operation, for the treatment of carcinoma of the upper and midthoracic portions of the esophagus. He advocated a three-stage operative procedure, the first stage being gastrostomy and removal of the lymph nodes of the celiac axis and paracardia. One week after the first surgical stage a total dose of radiation varying from 2,000 to 2,500 rads, given in four to five sessions of 500 rads each, (Cobalt 60) is given. Several days after the completion of irradiation, a total thoracic esophagectomy and cervical esophagostomy are performed as the second stage. A third stage antethoracic esophagogastrotomy is usually performed six months after the first stage.

In patients with cancer of the upper and midthoracic esophagus treated by radiation and operation, the four-year survival rate was 31.8 percent, compared with 15.4 percent in patients treated by resection only. There was very little change in morbidity or mortality.

Cliffton<sup>3</sup> and coworkers reported on 20 patients with esophageal cancer who had received a full course of preoperative radiation therapy. In 11 of these patients resection was carried out and it was found that the cancers had regressed considerably, in some cases had disappeared.

Watson,<sup>21</sup> using only external radiation therapy, obtained good results in the treatment of cancer of the upper two-thirds of the esophagus. Radiation therapy was begun in 16 and completed in 14 of 21 consecutive cases of cancer in this location. Four of the irradiated patients lived five or more years and three were still alive at the time of the report.

#### *In Laryngopharyngeal Cancer*

Lederman<sup>10</sup> expressed the opinion that most patients with early, localized laryngopharyngeal cancer can be given a preliminary course of radiation therapy, using "curative" doses, with hope for cure. For the more advanced cases he preferred preoperative radiation therapy when operation is indicated. He believed that with the blood supply intact there is a greater opportunity to shrink the cancer, to destroy or render the cancer cells less likely to proliferate and cause metastasis or recurrence at the site of the wound.

The effect of radiation on the supporting tissues and on the blood supply of the tumor bed are important. It is possible that the resistance may be affected but this is difficult to determine. There is an increase in the collagen and the hyalinization of the connective tissue. The blood supply is reduced because of the changes in the endothelium. The reduction in the lymph and blood supply can act as a deterrent to the spread of tumor cells.

Silverstone<sup>17</sup> and coworkers said they believed radical operation would offer a better prognosis for patients with advanced cancer of the laryngopharynx if the peripheral portion of the tumor could be reduced in extent so that the operative procedure would be the equivalent of an operation for an early lesion instead of an advanced lesion. They recommended preoperative radiation therapy in order to destroy or render non-reproductive the peripheral portion of the tumor, with operation following in about three weeks, before the recovery of growth activity of the remaining cancer cells. A tumor dose of 5,500 rads in about five weeks, a rest interval of three to six weeks, and then radical operation was recommended. Megavoltage therapy (Cobalt 60) was used. They en-

countered no technical difficulties and the wounds, without complications from infection or fistula information, all healed completely. Twenty-one patients with advanced cancer of the laryngopharynx, all stage III, completed a course of combined therapy and 16 had survived for periods from five to fifty-one months at the time of report. These investigators have continued the combined program on the basis of the favorable results obtained.

### *In Breast Cancer*

There are not yet enough clinical data available to assess the value of preoperative radiation therapy in the treatment of operable breast cancer. If there are no problems, concerning operability (the tumor is small and there is no skin involvement and no metastasis) preoperative radiation therapy probably should not be done; it should be reserved for patients with large tumor mass, involvement of the skin and on the borderline of operability.<sup>13,14</sup>

### *In Carcinoma of the Bladder*

Because cystectomy alone for bladder carcinoma has not produced sufficiently favorable five-year survival rates, DeWeerd<sup>4</sup> and Colby have studied the effects of combining the procedure with preoperative radiation therapy. One group of patients with infiltrating transitional or squamous cell carcinoma were given preoperative radiation to the bladder region, using either external Cobalt 60 or 6 Mev x-rays. The total tumor dose was about 4,800 rads given in two sessions, each session consisting of 2,400 rads delivered in a period of 12 to 14 days with a rest interval of three weeks. Total or segmental cystectomy and partial lymphadenectomy were carried out six weeks after the second irradiation. No residual intact cancer cells could be found in nine surgical specimens. There was no increase in postoperative complications, morbidity or mortality.

A second group of patients with infiltrating bladder tumors received a total tumor dose of from 1,800 to 2,400 rads given to the bladder region during three consecutive days at the rate of 600 rads daily, and then total or segmental cystectomy and partial pelvic lymphadenectomy immediately afterward. There was no increase in morbidity, mortality or complications.

Using radiation therapy (tumor dose of 3,500 rads given at the rate of 200 rads tumor dose daily to the bladder region), plus 5-fluorouracil (5-FU),

and then operation, Kaufman and Stein<sup>9</sup> treated 71 patients who had bladder tumors of various orders. Seven of nine patients who had recalcitrant Stage A tumors and eight of fifteen patients with Stage B1 lesions were tumor-free; and the resected specimens of bladders from seven of twenty patients with Stage B2 and C tumors were tumor-free. Five patients with Stage D1 or D2 tumors had lived more than two years at the time of the report, and three had lived reasonably comfortably for more than four years. This study is continuing.

### *In Cancer of the Head and Neck*

Early diagnosis or recognition of malignant lesions involving the head and neck while in a localized stage is most important, for a high proportion can be cured by operation, by radiation therapy or by a combination of the two. Yet in a surprising number of cases malignant disease in this region is in advanced stage when first diagnosed. This is probably due in part to inadequate routine examinations of the head and neck region, by neglecting biopsy of suspicious lesions, and sometimes by the patient's delay in consulting a physician. It should be noted in this regard that painful lesions are sometimes treated with antibiotics and if the symptoms improve, considerable time may elapse before biopsy is done and definitive treatment begun.

After the diagnosis is made and the extent of the disease determined the first physician who makes the decision as to the method of therapy bears the responsibility for the outcome. If the therapy selected is inadequate or not appropriate, subsequent therapy will be much less effective.

The primary lesions may initially produce few if any symptoms, and the first indication of disease may be the presence of metastatic disease in the nodes of the neck. For example, a high proportion of patients with primary cancers of the nasopharynx have metastatic disease in the neck when first seen. If an enlarged lymph node suspected of containing metastatic disease is present when the patient is first seen, the head and neck regions should be thoroughly examined (repeatedly if necessary) before the node is removed for biopsy. Not to do so may delay treatment of the primary cancer, making subsequent radical neck dissection more difficult and increasing the likelihood that the operative area will be "seeded" with tumor cells.

Millburn<sup>12</sup> and Hendrickson evaluated all of the 409 patients with primary disease in the oral

pharyngeal or laryngeal areas (squamous cell carcinoma) who had radical neck dissection at Presbyterian-St. Luke's Hospital. There were 163 patients in the group who had microscopically positive lymph nodes in the neck. Radical neck dissection alone was performed in 112 patients, and 28 of them (25 percent) were free of disease at the end of two years. Preoperative radiation therapy and planned radical neck dissection were carried out in 51 patients, and 46 of them (90.2 percent) were free of disease in the neck at the end of two years. The same surgeons were involved in both groups of patients. When there was recurrence, the interval between operation and the re-appearance of cancer was essentially the same: for operation only it was eight months; with combined therapy, five months. None of the patients with initially positive lymph nodes who survived free of disease for two years ever had recurrence in the treated area.

Strong<sup>20</sup> and coworkers reported the results of a cooperative controlled study of preoperative x-ray therapy as an adjunct to radical neck dissection. Only patients with histologically confirmed epidermoid or squamous cell cancer, primary in the head and neck region, and who had no previous operative or radiation therapy to the neck other than needle aspiration biopsy or tracheostomy, were included. The most common primary tumor sites in this group were tongue, floor of the mouth and extrinsic or supraglottic larynx. The technique of preoperative radiation was to use a single lateral port extending from the mastoid area to the chin, mandible and clavicle, with 400 R given daily for five days for a total dosage of 2,000 R. Operation was performed the day of the final treatment or as soon afterward as feasible. Megavoltage therapy was used. Patients who were born on even-numbered birthdays received no preoperative radiation to the neck and constituted the control series. Among patients with positive nodes, 30.9 percent of the treated group and 50 percent of the controls had recurrence in the neck. In the group with

negative nodes, none of the treated group and 7.8 percent of the controls had recurrence in the neck. Strong pointed out that the incidence of local recurrence of metastatic cancer in the neck following radical neck dissection in the treatment of cervical lymph node metastasis from primary head and neck cancers usually varied from 26 to 29.8 percent.

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